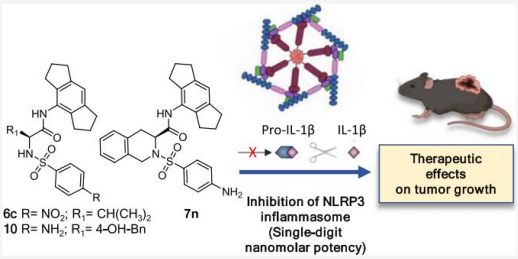
上海珂臻医药科技有限公司

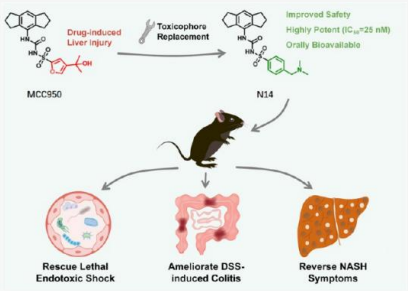
J. Med. Chem. 2023, 66, 5223−5241

ABSTRACT: The NLRP3 inflammasome is a critical component of innate immunity that senses diverse pathogen- and host-derived molecules. However, its aberrant activation has been associated with the pathogenesis of multiple diseases, including cancer. In this study, we designed and synthesized a series of aryl sulfonamide derivatives (ASDs) to inhibit the NLRP3 inflammasome. Among these, compounds **6c**, **7n**, and **10** specifically inhibited NLRP3 activation at nanomolar concentrations without affecting the activation of the NLRC4 and AIM2 inflammasomes. Furthermore, we demonstrated that these compounds reduce interleukin-1β (IL-1β) production *in vivo* and attenuate melanoma tumor growth. Moreover, metabolic stability in liver microsomes of **6c**, **7n**, and **10** was studied along with plasma exposure in mice of the most interesting compound **6c**. Therefore, we generated potent NLRP3 inflammasome inhibitors, which can be considered in future medicinal chemistry and pharmacological studies aimed at developing a new therapeutic approach for NLRP3 inflammasome-driven cancer.

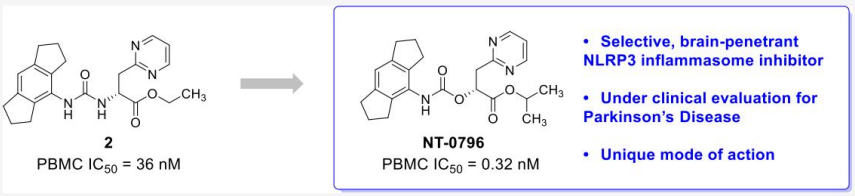


J. Med. Chem. 2023, 66, 12966−12989

ABSTRACT: The NLRP3 inflammasome is a critical component of innate immunity involved in the pathophysiology of various inflammatory diseases. In this study, we designed and synthesized a series of NLRP3 inflammasome inhibitors based on MCC950. Specifically, we optimized the furan moiety, which is considered to be potentially associated with drug-induced liver injury. The representative inhibitor **N14**, 4-(2-(dimethylamino)ethyl)-*N*-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)benzenesulfonamide, not only maintains the NLRP3 inhibitory activity of MCC950 with IC_{50} of 25 nM but also demonstrates improved tolerability in human hepatic cells line and mouse primary hepatocytes. In addition, **N14** exhibits superior pharmacokinetic properties, with an oral bioavailability of 85.2%. *In vivo* studies demonstrate that **N14** is more effective than MCC950 in multiple NLRP3-related animal model diseases, including nonalcoholic steatohepatitis, lethal septic shock, and colitis. Our research has provided a lead compound that directly targets the NLRP3 inflammasome and can be developed as a novel therapeutic candidate for NLRP3-driven diseases.



J. Med. Chem. 2023, 66, 14897−14911



ABSTRACT: The NLRP3 inflammasome is a component of the innate immune system involved in the production of proinflammatory cytokines. Neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis, have been shown to have a component driven by NLRP3 inflammasome activation. Diseases such as these with large unmet medical needs have resulted in an interest in inhibiting the NLRP3 inflammasome as a potential pharmacological treatment, but to date, no marketed drugs specifically targeting NLRP3 have been approved. Furthermore, the requirement for CNS-penetrant molecules adds additional complexity to the search for NLRP3 inflammasome inhibitors suitable for clinical investigation of neuroinflammatory disorders. We designed a series of ester-substituted carbamate compounds as selective NLRP3 inflammasome inhibitors, leading to **NT-0796**, an isopropyl ester that undergoes intracellular conversion to **NDT-19795**, the carboxylic acid active species. **NT-0796** was shown to be a potent and selective NLRP3 inflammasome inhibitor with demonstrated *in vivo* brain penetration.

J. Med. Chem. 2022, 65, 14721−14739

ABSTRACT: Inappropriate activation of the NLRP3 inflammasome has been implicated in multiple inflammatory and autoimmune diseases. Herein, we aimed to develop novel NLRP3 inhibitors that could minimize the risk of drug-induced liver injury. Lipophilic ligand efficiency was used as a guiding metric to identify a series of 6,7-dihydro-5H-pyrazolo[5,1-*b*][1,3]-oxazinesulfonylureas. A leading compound from this series was advanced into safety studies in cynomolgus monkeys, and renal toxicity, due to compound precipitation, was observed. To overcome this obstacle, we focused on improving the solubility of our compounds, specifically by introducing basic amine substituents into the scaffold. This led to the identification of GDC-2394, a potent and selective NLRP3 inhibitor, with an in vitro and in vivo safety profile suitable for advancement into human clinical trials.